JACC Vol. 27, No. 5
April 1996:1198–200

Editorial Comment

Heart Transplant Centers: No Longer the End of the Road for Heart Failure*

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Improving survival on medical therapy. The impact of medical therapy for advanced heart failure continues to improve, as demonstrated in the article by Rickenbacher et al. (1) from Stanford University, whose experience also emphasizes the limited prognostic factors and the critical importance of concentrated expertise for this population. No longer are patients referred for transplantation given a prognosis of <6 months to live with their original hearts. With this and other recent experience, we have now passed far beyond the study that concluded in 1985 that patients initially considered "too well" for transplantation subsequently deteriorated and died (2), without the meticulous follow-up and reevaluation that have since been recognized as a pivotal component of successful outcome, with or without transplantation. Even patients discharged after presenting for transplantation with New York Heart Association functional class IV symptoms have recently been shown to have a 1-year survival of 68% (3), compared with the earlier 54% described in 1987 for the enalapril group of the CONSENSUS trial (4) in patients with less clinical compromise.

The Stanford center's experience of 116 patients with mean peak oxygen uptake (Vo_2) of 17 ml/kg per min confirms reports by Mancini et al. (5) and Stevenson (6) that potential transplant candidates with peak Vo_2 >12 to 14 ml/kg per min have good 1- to 2-year survival without transplantation. The current report provides further follow-up >2 years for a sizeable group of patients eligible for transplantation, demonstrating the continued similarity to results after transplantation, although transplantation still provides better late survival (60% to 70% at 5 years, 45% at 10 years [7]). This group of patients should not expect significant improvement in functional capacity after transplantation, at least as measured by peak Vo_2, which remains in the range of 50% to 70% of predicted normal values after transplantation. A randomized, controlled trial between transplantation and medical therapy has been suggested for patients with peak Vo_2 >13 ml/kg per min, but such a trial is unlikely to occur in the current era, as defined by 1) the priority of more critically ill patients for limited donor hearts, and 2) the guidelines from both the Bethesda Conference (8) and the Consensus Conference on Candidate Selection (9) suggesting that transplantation is not often indicated for patients with peak Vo_2 >14 ml/kg per min.

Identification of high and low risk patients. There are extensive published reports addressing the risk factors for poor outcome in heart failure. Many risk factors validated in the broad spectrum of mild to moderate heart failure are uniformly elevated and are thus poor discriminants in advanced heart failure. As presented in the report by Rickenbacher et al. (1) and others, attempts to define a population at particularly low risk may be more relevant to the evaluation of individual ambulatory candidates for heart transplantation. This reports the successful integrated decision process of an experienced transplant center, but their success cannot be translated into guidelines by which effective selection could be made with less experience. However, it is not necessarily desirable that selection for transplantation take place without extensive experience.

Having already defined a group at relatively low risk using multiple factors, Rickenbacher et al. then searched for factors within that group that would predict higher risk among the low risk patients. The small numbers of end points (eight cardiac deaths, eight later listings for transplantation) limit attempts to validate these risk factors. The variables of longer symptom duration and elevated pulmonary pressures predicted need for transplantation but also could have contributed to the decision regarding need for transplantation. The lack of contribution of peak Vo_2, in contrast to other reports, probably reflects its contribution to selection of the original cohort with an average peak Vo_2 of 17 ± 4 ml/kg per min, which would predict a favorable outcome. Multiple other prognostic factors have been proposed in the population with advanced heart failure (Table 1). Once left ventricular ejection fraction is <30% and heart failure is advanced, the measured value of left ventricular ejection fraction has not been predictive in the Rickenbacher et al. or most other recent studies, although some controversy exists. Right ventricular function is less uniformly compromised and may in future be found to confer more prognostic information (10).

This and multiple recent studies emphasize the importance of serial evaluation of patients after initial referral, at which time their condition may reflect more the vigor of previous therapy than the underlying capacity for compensation. The Bethesda Conference summary describes the need for aggressive therapy with combinations of vasodilator and diuretic drugs before assessment of indications for transplantation, indicating that "therapy should be adjusted until clinical congestion has been resolved or until further therapy has been repeatedly limited by severe hypotension (generally systolic blood pressure <80 mm Hg) or marked azotemia" (8). It is further emphasized that "Patients should not be considered to have refractory hemodynamic decompensation until therapy

*Editorials published in *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

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0735-1097/96/$15.00
SSDI 0735-1097(95)00604-4

Table 1. Partial List of Proposed Prognostic Factors in Ambulatory Candidates for Heart Transplantation

Common prognostic factors
Clinical status
New York Heart Association functional class
Criteria of stability
Peak oxygen consumption
Demonstrable improvement or deterioration
Left ventricular dimension
Right ventricular function
Atrioventricular regurgitation
Pulmonary pressures/filling pressures on optimal therapy
Systemic blood pressure
Serum sodium concentration
Ability to take angiotensin-converting enzyme inhibitors
Factors predictive in some series
Etiology of disease
Duration of disease
Left ventricular ejection fraction
Cardiac index
Serum catecholamine levels
History of symptomatic/asymptomatic arrhythmias
Factors with limited information
Degree of myocardial fibrosis
Atrial natriuretic peptide levels
Endothelin levels
Cytokine levels
MIBG imaging of myocardium
Reduced ratio of tri-iodothyronine/reverse tri-iodothyronine
Abnormal findings on signal-averaged electrocardiogram
Numerous others described in small series

MIBG = metaiodobenzylguanidine.

with intravenous followed by oral vasodilator and diuretic agents has been pursued using continuous hemodynamic monitoring to approach hemodynamic goals." In the approach presented by Rickenbacher et al., the 18% of referred patients ultimately classified as "too well" achieved similar hemodynamic and clinical goals through serial outpatient adjustments of therapy. Whether more aggressive inpatient therapy could have restored stabilization in any of the 35% of their patients initially listed for transplantation or the 25% of patients rejected for transplantation is not known.

One of the strongest predictors of good outcome may be improvement after referral (11). A minority of patients may actually have spontaneous improvement of left ventricular function as a result of resolution of cardiomyopathy of relatively recent onset, recent viral illness exacerbating left ventricular dysfunction of another cause or abstention from heavy alcohol consumption. These patients may need to be identified and followed up differently than those with a stable low ejection fraction (12). However, even without major improvement in left ventricular ejection fraction, clinical improvement frequently occurs, as defined by criteria for freedom from congestion, increase in peak Vo_2 or improvement in the global assessment of quality of life, as discussed in the report by Rickenbacher et al.

In an earlier era of transplantation and medical therapy, the "wait and see" strategy of selection was shadowed by the relatively high risk of sudden death early after referral. Although sudden death continues to account for up to 50% of mortality in many studies and all of the mortality in the present study (1), the absolute incidence has decreased. The increasing use of angiotensin-converting enzyme inhibitors, the avoidance of class I antiarrhythmic agents and perhaps increasing use of amiodarone appear to have contributed to the improved survival in advanced heart failure. In a recent longitudinal study of 737 patients referred for transplantation (13), the 1-year risk of sudden death on medical therapy declined from 20% before 1988 to 8% after 1990. It should be recognized that some of the decrease in sudden death may also result from the closer surveillance and improving ability to recognize and address early signs of recurrent hemodynamic decompensation. The most common adverse event after the first 6 months is no longer death; rather, it is deterioration to the point of requiring urgent transplantation (14). In this and other experience, such deterioration is not associated with a worse posttransplant outcome but will increase overall hospital costs.

Heart failure/transplant centers—new destinations. The increasing success of transplantation has attracted large numbers of patients with advanced heart failure. Although these potential candidates have come to transplant centers as "the end of the road," the supply of donor hearts cannot begin to match the need. Approaches originally developed just to keep patients going until transplantation have now evolved to provide alternate routes for many patients to defer or even avoid transplantation. A vital component of the success of every program has been the recognition that the same investment in facilities and personnel necessary for a successful transplant program or clinical trial program is necessary for optimal care of all patients with advanced heart failure. It is particularly encouraging in this financially constrained system that cost savings can be demonstrated for potential transplant candidates in terms of up to an 80% decrease in hospital admissions for heart failure after referral to a transplant center (15). Such savings might be extended by referral of patients after the first hospital admission rather than waiting until heart failure appears to be "end-stage." Decreased cost and improved quality of life also resulted from specialized intervention in elderly patients with milder heart failure (16).

In current practice, patients are seldom referred for care of heart failure unless transplantation is considered to be an eventual option. However, should the benefits of heart failure/transplant centers be restricted to potential candidates for transplantation? There will be ~2,400 patients receiving a heart transplant this year, whereas >1 million patients will be admitted to the hospital with heart failure. For the majority of these patients who are beyond the age limit for heart transplantation, there is currently little opportunity to benefit from the lessons learned at heart failure/transplant centers. The most important new mission of the dedicated heart failure/transplant centers may be to offer measurably better quality of life to the growing populations of patients with heart failure for whom transplantation will never be an option.

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April 1996:1198–200

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